REMARKS

In the final Office Action mailed April 23, 2007, Claims 29-33 were rejected as anticipated by US Publication No. 2002/0141994, and Claims 29, 30 and 34 were rejected as obvious over this same publication in combination with certain US patents. The Examiner indicated that the US Publication continued to qualify as prior art despite the Rule 131 Declaration submitted by Applicants because the subject matter of the US publication and that of the present application were not patentably distinct.

The application that is the subject of US Publication No. 2002/0141994 has now been granted as US Patent No. 7,108,852. All of the claims of this granted patent have been amended from those of the US publication, and are limited to the use of "an antibody to a M-CSF." In contrast, all of the presently pending claims are now directed to the use of an antibody specific for GM-CSF. The Examiner agreed at the interview that the recitation of these different antibodies patentably distinguished the claims of the present application from those of US Patent No. 7,108,852. Accordingly, the Rule 131 Declaration previously submitted by Applicants can now be accepted to establish that the subject matter of the present invention was invented prior to the filing date of the application published as US Publication No. 2002/0141994. As a result, US Publication No. 2002/0141994 no longer qualifies as prior art and the rejections should be withdrawn.

Applicant wishes to note that US Publication No. 2007/0059280 is the publication of U.S. Application No. 11/519,502, filed September 12, 2006, which is a continuation of the application published as US Publication No. 2002/0141994. This publication has claims which appear to be quite similar, if not identical, to those in US Publication No. 2002/0141994. Based on the record available from the USPTO's PAIR database, the published claims appear to remain pending. Only two of the 27 claims in this publication recite GM-CSF, Claims 10 and 27. In the restriction requirement dated September 10, 2002 in the earlier application, Claim 10 appeared in Groups IX, X and XI, while Claim 27 appeared in Group XIX. The claims pending in the present application are most closely related to the "methods of treating" of Groups XV and XVI of that restriction requirement. Thus, the USPTO has already determined that the claims of the present application are directed to an invention distinct from those of Claims 10 and 27. As such, the Rule 131 Declaration is also effective to overcome any rejection that might be based on US Publication No. 2007/0059280.

An Information Disclosure Statement listing the references discussed at the interview, along with additional references, accompanies this Amendment. As requested by the Examiner, a Declaration by inventor, Gary Anderson, is provided herewith. The Declaration discusses certain of the references cited in the Information Disclosure Statement. Applicants wish to note that the Examiner is requested to review all of the references cited in the Information Disclosure Statement, and not just those referred to in the Declaration, as no implication is intended that the references not referred to in the Declaration are not relevant to the prosecution of the present application. Additionally, the Examiner should be aware that the various characterizations of the references made by the inventor in the Declaration are not intended to represent the entirety of the teachings of the references. As such, the Examiner is respectfully requested to review all of the references in their entirety.

The Declaration is submitted based on the request made by the Examiner at the interview. This Declaration evidences the patentability of the presently pending claims, including newly added Claims 39-64.

In view of the amendments to the claims and the foregoing remarks, the present application is believed to be fully in condition for allowance. However, should the Examiner identify any impediments to the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned attorney at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 21 Aug. 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Hamilton et al.
Appl. No.	:	09/851,230
Filed	:	May 8, 2001
For	:	METHOD OF TREATMENT AND AGENTS USEFUL FOR SAME
Examiner	:	M. Belyavskyi
Group Art Unit	:	1644

DECLARATION OF GARY P. ANDERSON, Ph.D.

1. I am co-inventor of the above-identified patent application. Although I received assistance from my attorneys in drafting this Declaration, the information herein represents my own opinions and understanding of the facts.

2. I am employed as a tenured full professor by the University of Melbourne, Australia, the assignee of the present application. I have a dual appointment in the Department of Pharmacology (50%) and the Department of Medicine (50%). I have been employed by the University of Melbourne for approximately 10 years.

3. Prior to my present appointment, I worked as a research scientist in the Swiss pharmaceuticals industry for approximately 9 years in Basel, Switzerland. In Switzerland, I worked for Ciba-Geigy Pharmaceuticals (now Novartis Pharmaceuticals for about 7 years) as a research scientist in the IBA ("Inflammation, Bone and Allergy") division. Before that I worked for about 1.5 years as a post doctoral research fellow in Sandoz Pharmaceuticals (now also Novartis Pharmaceuticals) in Basel, Switzerland. Prior to that I completed my doctoral studies at the University of Melbourne after my undergraduate studies where I graduated with a 1st class Honors degree in Pharmacology at the head of my class.

4. I have read and understood the specification and figures of the present applications. I have also reviewed the pending claims as amended in the accompanying Amendment. These claims relate generally to a method for ameliorating the effects of inflammation in a subject, which comprises administering an antibody specific for GM-CSF to the subject for a time and in an amount to inhibit or otherwise antagonize the effects of GM-CSF on cells of the monocyte or macrophage lineage. In certain of the claims, the inflammation is chronic inflammation. In other claims, the subject is exhibiting inflammation or in need of treatment for chronic inflammation.

5. On June 15, 2007, I attended an in-person interview with Examiner Belyavskyi. At this interview, various prior art references were presented. I provided an oral summary of this prior art to the Examiner, who then asked whether I could provide a written declaration in which I describe what I regard as the teachings of such prior art and whether, in my view, any would teach or suggest the claimed invention. Accordingly, the following paragraphs provide my characterization of certain teachings of some of the prior art references. For convenience, I have grouped each prior art reference into one of six categories areas, as described below.

6. have grouped 4 prior art references into a first category I describe as teaching that GM-CSF-like activity and/or GM-CSF is present as a component of the mixtures of growth factors that can be detected in biological fluids recovered from diseased individual and/or from supernatants of cells and/or tissues cultured from such patients.

a. Williamson et al. (1) reported in 1998 that multiple CSF (colony stimulating factor) biological activities were present in synovial fluid from arthritis patients. This paper referred to "GM-CSF-like," "G-CSF-like" and "M-CSF-like" bioactivities. The paper is noteworthy because it showed a very wide distribution of colony stimulating activities during progressive elutriation and little of the total activity correlated with the elutriation profile of authentic GM-CSF. The results point to multiple factors being involved in arthritis and do not favor GM-CSF as a dominant contributor to disease. The authors conclude "It is likely that synovial fluid contains a mixture of CSF" and the full range of activities exhibited by the synovial fluid samples "can not be ascribed to any one of the known human CSF acting in isolation". As such, the authors inferred from their findings that it would be necessary to block multiple factors concurrently if their effects were to be reduced in vivo.

b. In the same year, 1989, in a similar study of rheumatoid synovial effusion fluid, Xu et al. (2) reported they were unable to detect GM-CSF by radio-immunoassay. They found a "GM-CSF-like activity," but noted that such activity was often blocked by an endogenous inhibitor that first had to be diluted away before the GM-CSF-like activity could be observed. This study, thus, indicates that GM-CSF may not be functionally active—even if detectable by a bioassay ex vivo—due to its suppression by an endogenous inhibitory factor or factors in vivo.

c. In similar studies in 1990, Leizer et al. (3) reported that interleukin-1-stimulated cultured human synovial fibroblasts, which were obtained from arthritis patients, produced GM-CSF and G-CSF as measured by ELISA and by bioassay.

However, in order to detect GM-CSF bioactivity (confirmed by a neutralizing antibody, LMM102), they found it was necessary to pre-enrich supernatants by immunoaffinity chromatography indicating that GM-CSF was present in a low concentration. Moreover, they found that neutralizing GM-CSF with LMM102 had no effect on IL-1-induced G-CSF production.

d. In another similar study in 1991, Alvaro-Gracia et al. (4) investigated GM-CSF production in two cell types from arthritis patients, fibroblast-like synoviocytes and synovial macrophages, and concluded that GM-CSF was absent in unstimulated fibroblast-like synoviocytes, while being found only in very small amounts in unstimulated synovial macrophages. This group further found that Tumor Necrosis Factor alpha (TNFα) and especially IL-1β were dominant and upstream inflammatory mediators that could induce GM-CSF in both cell types. Together, these data demonstrate that GM-CSF is a minor and downstream cytokine (vis-à-vis TNFα and IL-1β), whose production is not intrinsically sustained. Earlier work from the same laboratory (2) had established that when synovial fluid from rheumatoid arthritis patients was studied, GM-CSF activity was often absent, as it was frequently complexed to a natural inhibitor, reinforcing the understanding that GM-CSF did not play a meaningful role in inflammatory states. This earlier reference is discussed in more detail above in subparagraph 5(b).

e. When considered together, the data from the papers discussed in this paragraph indicate: that cytokines other than GM-CSF (such as TNFα and IL-1β) are the dominant inflammatory mediators in arthritis; that a GM-CSF-like activity is present only in low concentrations during an inflammatory state, requiring pre-enrichment to study; that GM-CSF (where it *can* be found) is a minor component of the total blood cell colony stimulating factors (CSFs) during an inflammatory state; and that detection of GM-CSF functional activity additionally may require removal of a GM-CSF inhibitor factor.

7. I have grouped 6 prior art references into a second category I describe as teaching that the effects on arthritis of exogenous recombinant GM-CSF administered to humans or rodents are highly variable and contradictory.

a. As recombinant GM-CSF was originally developed to restore depleted white cell blood count in leukopenic patients, it has been used extensively in the clinic. In 1991, de Vries et al. (5) reported that a leukopenic patient receiving chemotherapy for stage III fallopian tube carcinoma, who had co-morbid arthritis,

reported increased joint stiffness and pain after subcutaneous injection of recombinant human GM-CSF administered to treat her leukopenia.

b. In 1989, Hazenberg et al. (6) reported a flare-up in arthritis in a febrile leukopenic Felty's syndrome patient (Leukopenia and arthritis are components of the condition called "Felty's syndrome") who received subcutaneous administration of human recombinant GM-CSF to treat a life-threatening infection. These findings were not uniformly replicated.

c. Lubbe et al. (7) found, however, that human recombinant GM-CSF did not cause a flare in arthritis in Felty's syndrome;

d. Further, Kaiser et al. (8) found that administered human recombinant GM-CSF actually improved arthritis in Felty's syndrome; and Krishnaswamy et al. (9) found that long-term administration of human recombinant GM-CSF did not worsen arthritis in Felty's patients.

e. In 1997, Campbell et al. (10) (some of whom are co-inventors of the presently claimed invention) reported that murine recombinant GM-CSF exerted an adjuvant-like effect in the induction of collagen induced arthritis in DBA/1 mice, but noted that results with exogenous GM-CSF could not be used to infer a role for endogenous GM-CSF in arthritis.

f. Taken together, these papers show that exogenous recombinant GM-CSF administered systemically by subcutaneous injection has highly variable and directly contradictory effects on patients suffering from arthritis or an arthritic-like condition. This is consistent with the insights into the biology of GM-CSF by its discoverer Metcalf (11), who stressed differences in the effects of GM-CSF administered systemically versus GM-CSF that might be produced locally. It is noteworthy that the clinical case reports are highly inconsistent and draw no inference on the role of endogenous GM-CSF in the pathogenesis of arthritis.

8. I have grouped 3 prior art references into a third category I describe as teaching that GM-CSF might affect neutrophil count or function acutely, but not chronically, in *in vivo* or *ex vivo* models. GM-CSF was discovered as a bioactivity able to induce granulocytes, predominantly neutrophils but also eosinophils and macrophages in colony assays; and GM-CSF is known to promote the survival and capacity for oxidative burst during host defense of these cells.

a. In 1994, Robertson et al. (12) found that phorbol ester TPA (12-O-tetradecanoylphorbol-13-aetate) applied topically induced transient induction of GM-

CSF mRNA in dorsal skin of a cancer-prone mouse strain (SENCAR mice). Re-administration of TPA led to diminished GM-CSF mRNA levels and direct injection of GM-CSF into the skin produced no inflammatory reaction. When administered intraperitoneally (but inexplicably not when administered intravenously or subcutaneously), GM-CSF enhanced neutrophil accumulation and dermal thickening in the skin in response to TPA, and these responses were diminished using a rabbit serum against GM-CSF. Responses in the skin were acute in nature and, hence, not sustained in this model. Also in these experiments, the serum against GM-CSF was administered prophylactically, i.e., prior to skin irritation with TPA, and the serum exerted no effect on chronic inflammation. To this end, macrophage numbers were not reduced by pretreatment with the serum; and induction of skin cancer, which the authors specifically state is dependent on inflammation, was not reported.

b. Also in 1994, Vasunia et al. (13) found that TPA also induced transient and diminishing GM-CSF mRNA responses in mouse skin. Neutralization of GM-CSF with a prophylactically-administered goat serum raised against GM-CSF had no effect on epithelial hyperplasia (an index linked to cancer induction) but diminished infiltrating leukocytes (neutrophils) at 24 hours, but not 48 hours post insult. No attempt was made to treat an established skin response caused by TPA, which is indicative of the very transient induction of GM-CSF and, hence, the short duration of neutrophil influx into the skin. At most, these data indicate that neutralization of GM-CSF, prior to the onset of injury but not afterwards, had an effect only on acute, not chronic, aspect of tissue responses to irritation with the phorbol ester TPA.

c. In 1994 Ilercus et al. (14) made mutated versions of GM-CSF having a substitution mutation at residue 21, which they proposed were able to bind to the specific alpha chain, but not the common beta chain (βc),of the GM-CSF receptor complex, without activating the complex. Two of these muteins, E21R and E21K, competed with very low affinity for GM-CSF at the alpha chain. E21R and E21K weakly competed against (requiring more than 70-fold molar excess) GM-CSF, but not TNFα, for induction of superoxide burst in neutrophils ex vivo. These data show that the blocking of GM-CSF function in vitro produced an acute suppression of neutrophil oxidative burst, albeit at extremely high doses of mutein. These data did not, however, suggest the feasibility of blocking endogenous GM-CSF effects in vivo, and further suggested that an effect if it we to be observed—would be restricted to the rapid transient effects on neutrophil oxidative burst.

d. Collectively, the data of Robertson and Vasunia indicate that chemical irritation of the skin with the known tumor promoter TPA leads to transient GM-CSF mRNA induction and neutrophil (but not macrophage) accumulation in the skin. GM-CSF induction of superoxide burst was also shown to be dependent on interaction with the GM-CSF receptor alpha chain. These data also indicate that GM-CSF acts transiently and that, when it does act, its target cell is a neutrophil; and the blockade of GM-CSF had to be made prior to onset of acute injury. The data in no way support the use of neutralization of GM-CSF to treat chronic inflammatory disease states, whether prophylactically or post-insult; neither do they suggest the ability to relieve an acute inflammatory state (not to mention a chronic inflammatory condition) by antagonizing transient-produced GM-CSF post insult

9. I have classified 2 prior art references into a fourth category I describe as teaching that GM-CSF does not play an active role in chronic inflammation because it may be inactivated by binding to a natural inhibitor and it may induce natural anti-inflammatory mechanisms.

a. As discussed above Xu et al. (2) found that GM-CSF recovered from arthritis fluids was often in a biologically inactive state, precluding its action in such diseases, because it was bound to a natural inhibitor which had first to be removed by extensive dilution before GM-CSF activity could be observed.

b. In 2000, Kinne et al. (15) reviewed the state-of-the-art on the role of macrophages in the pathogenesis of rheumatoid arthritis. They also reviewed each of the therapeutic concepts thought to be important as a possible future treatment for rheumatoid arthritis. They cover the central roles of IL-1β, TNFα and IL-6. They discuss the pathogenic roles of IL-15, IL-17 and IL-18, as well as the potential beneficial roles of IL-4, IL-10, IL-11, IL-13 and IL-16. Specifically, Kinne and colleagues did not identify GM-CSF as a therapeutic target to treat rheumatoid arthritis; rather, Kinne stated the opposite, namely, that GM-CSF is a cytokine that limits inflammation by inducing IL1RA (IL1receptor antagonist is the potent natural endogenous antagonist of IL-1). This information suggests that GM-CSF would exert an anti-inflammatory role in vivo.

10. I have grouped 3 prior art references into a fifth category I describe as teaching away from blocking GM-CSF to treat inflammatory diseases.

a. Dunn et al. (16) first reported in 1994 on the characteristics of mice where the gene for GM-CSF had been inactivated by homologous recombination gene

targeting (called GM-CSF deficient mice, GM-CSF knock-out mice or GM-CSF KO mice), (16). Dunn's group additionally reported that these mice were susceptible to serious bacterial and mycobacterial infections. Furthermore these mice developed a fatal lung disease called alveolar proteinosis.

b. Separately, Paine et al. (17) note that GM-CSF deficient mice also develop an inflammatory lung condition, now understood to be due to compensatory up-regulation of the growth factor M-CSF and the chemokine MCP-1

c. The findings of Dunn's group (16) were replicated by Dranoff et al. (18) in a very prominent Science paper, suggesting that endogenous GM-CSF is redundant *in vivo* and even has an anti-inflammatory role. Like Dunn's group Dranoff and colleagues found extensive lymphocytic inflammation in GM-CSF deficient mice.

d. Dranoff et al. (18) found that inflammation in GM-CSF-/- mice was not due to lung infection. They further suggest that GM-CSF acts to limit inflammation at the level of macrophages (because they show GM-CSF regulates macrophage development), which I interpret as being the opposite of the presently claimed invention: They, thus, concluded, "It is possible that the lymphoid hyperplasia represents an excessive response to innocuous inhaled antigens. Alveolar macrophages are known to inhibit mitogen-induced lymphocyte proliferation in vitro and perhaps function to buffer the lung from toxicities associated with inflammation."

11. A sixth category of references relates to the fickle and highly unpredictable effects of anti-cytokine antibodies in *in vivo* disease models. My co-workers and I have shown that an anti-IL-4 antibody, called 11B11, prevented, but could not treat established, experimental asthma in mice (19). Finkelman had studied the properties of 11B11 and had shown that, although it was a "neutralizing" antibody, it enhanced disease by acting as a reservoir effectively extending the duration of action of IL-4 and worsening its effects in vivo (20, 21). Finkelman also extended these findings to IL-3 and IL-7 suggesting this to be a general phenomenon (20-22).

12. In summary, at the time of our invention, the balance of evidence suggested that GM-CSF was one of many blood growth factors detectable in material from arthritis patients, and that other cytokines, notably IL-1β and TNFα, were directly linked to disease pathogenesis; that exogenous GM-CSF produced transient and inconsistent effects on human arthritis; that skin irritation with TPA in cancer models induced transient and weak GM-CSF expression associated with transient neutrophil infiltration; that interventions directed against GM-CSF using antisera or muteins affected neutrophils and were employed only in acute

prophylactic but not therapeutic approaches for chronic disease states; that GM-CSF-KO mice indicated that blocking GM-CSF would have serious and potentially fatal adverse effects; and, that the general biology of antibodies and cytokine treatment indicated that the result of blocking cytokines was unpredictable in *in vivo* disease models. Thus, it is my view that the prior art would not have suggested to a person having ordinary skill in this area the effects of inflammation in a subject could be ameliorated by administering an antibody specific for GM-CSF to the subject. In particular, there would be no such suggestion in regards to chronic inflammation or in the treatment of subjects already exhibiting inflammation.

13. Moreover, it is clear from the foregoing that the literature on the biology of GM-CSF contained many contradictory findings. My colleagues and I addressed GM-CSF's role experimentally to resolve this matter. In our research work, we specifically asked the question of whether a monoclonal antibody that neutralized GM-CSF could be administered therapeutically, i.e., after induction of disease, to treat established chronic inflammation.

14. It is my view that at the time we made our invention, the balance of evidence would have lead to great doubt that blocking GM-CSF would be beneficial for the treatment of inflammatory diseases. Indeed, I was personally highly skeptical of the potential to treat inflammatory disease by blocking GM-CSF with antibodies and I was greatly surprised at the efficacy of antibodies against GM-CSF in in vivo disease models.

15. In view of this surprising outcome and the backdrop of great doubt, it is my view that the prior art would not have suggested one having ordinary skill in this area would not have had a reasonable likelihood of success in ameliorating the effects of inflammation in a subject by administering an antibody specific for GM-CSF to the subject. This is especially true in regards to chronic inflammation or in the treatment of subjects already exhibiting inflammation.

Respectfully submitted,

Dated: 16 August, 2007

By: _____
Gary P. Anderson, Ph.D.

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Filed : May 8, 2001

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